Review Article

Clinical effect of metformin in children and adolescents with type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

To assess the clinical value and of metformin as mono-therapy versus other treatments for type 2 diabetes mellitus in children and adolescents. Major electronic databases, the reference lists of relevant articles and databases of ongoing trials were searched. Authors of reviews and metformin manufacturers were contacted in order to obtain more references and reports of unpublished trials. The methodological quality of these reports, included randomised controlled trials (RCTs) was assessed using the National Health System Centre for Reviews and Dissemination (NHS CRD) checklist. The search identified 1,825 studies. Three RCTs met the inclusion criteria. Two RCTs had been completed and one was still ongoing. In the metformin group there were significant reductions of mean change of HBA1c from baseline. It reduced by -0.71% (P = 0.0002) and in the other trial the result was reduced by -1.10 (95% CI: -1.19 to -1.01). In addition, more patients (48.1%) in the metformin group achieved good glycaemic control (<7%) at week 24. The mean changes in FPG from baseline were significantly (P < 0.05) different in the metformin group (-16.6%, for week 18 and week 24 20.6%. In the second trial there was a significant (P < 0.001) reduction in the adjusted mean of FPG from baseline in the metformin group, while there was an increase in the placebo group (-42.9 mg/dl vs. +21.4mg/dl) with mean difference of -64.80 in favour of the metformin group. For BMI, significant (P < 0.001) differences were seen at week 12 and week 24 (0.07 and 0.55 kg^2) for metformin and glimepiride respectively. There was no significant difference between the placebo and metformin in the other trials. For lipid value there was a significant decrease in LDL levels in the metformin group. No significant changes were found in the other lipid parameters after adjusting. There were more adverse events in the metformin group but they were not statistically significant. There was a limited but not convincing evidence to suggest that metformin can improve the glycaemic control in children and adolescent with type 2 diabetes compared with other interventions. This is may be the result of the limited number, poor quality and short duration of the included trials.

Key Words: Adolescents, children, diabetes mellitus, meta-analysis, metformin, systematic review

INTRODUCTION

Type 2 diabetes mellitus (T2DM) in children has increased dramatically in recent years, due to several factors such as obesity, change in lifestyle and diet problems.[1] Evidence from the USA, Japan, Austria and France shows a worldwide spread of T2DM in children.[1] In adults, metformin is effective as mono-therapy to improve glycaemia control, with a low risk of hypoglycaemia, and with independent benefits of little weight gain and improved lipid levels.[2,3] It is important to note that few safety and effectiveness studies have been conducted in the paediatric population.[2,3] Insulin is approved for use among children. Metformin has an advantage over insulin of producing less hypoglycaemia and being non-injectable. The T2DM may have earlier and more aggressive complications in paediatric patients.[4] Adherence to long-term therapies such as diabetes management requires simplifying the regime; for example, it is better to have less frequent dosing and a non-injectable form. This option may enhance patients' compliance with

oral therapy compared to other conventional treatments. It may also lead to better metabolic control.

There is no systematic review currently in this area. But there is a systematic review on metformin in the management of T2DM in adults, published in the Cochrane Database.[5] It concluded that Metformin may be the first treatment option in T2DM with obesity, as it may prevent various vascular complications, and mortality.[5] It produces favourable changes in glycaemia control, and moderate changes in lipids, weight, and diastolic blood pressure.[5] Diet, insulin thiazolidinediones, alpha-glucosidase inhibitors, meglitinides and Sulphonylureas failed to prove more advantageous for glycaemia control, lipid, or body weight than metformin.[5]

This systematic review was carried out to assess the clinical effectiveness of metformin as mono-therapy versus (vs.) other treatments for T2DM in children and adolescents.

MATERIALS AND METHODS

Type of studies
Trials and studies were included only if they were randomised control trials (RCTs). Quasi-randomised and non-randomised studies were excluded.

Type of participants
Children (2 to 12 years) and adolescents (12 to 18 years) with T2DM, according to the established diagnosis using valid standard criteria, such as WHO 1999 criteria,[6] or the American Diabetes Association (ADA) criteria.[2] Exclusion criteria were: any evidence of one or more positive immune markers for type 1 diabetes mellitus (T1DM) and age above 18 years.

Type of intervention
Metformin (extended release or immediate release) vs. other treatments of T2DM in children such as diet, exercise, insulin, or other oral hypoglycaemic agent were accepted. Studies using combined drugs treatment in the intervention group and studies with less than four weeks of exposure to treatments (to allow the stabilization of glycaemic control) were excluded.

Type of outcome
Primary outcomes
1. Glycaemic control (as measured by glycosylated haemoglobin A1c (HBA1c).
2. Diabetes related complications.
3. Adverse effects such as lactic acidosis, hypoglycaemia, hyperglycaemia, withdrawal due to adverse effects, and gastrointestinal side effect.

Secondary outcomes
All-cause mortality, compliance, health-related quality of life: physical activity/participation in physical activity, psychological factors/psychological wellbeing, including self-esteem, quality of life, diabetes knowledge, psychosocial factors, school participation/absence.

Search strategy
The Cochrane Library (until May 2008), Ovid MEDLINE (from 1950 to May Week 4 2008), EMBASE (from 1972 to 2008 Week 23), International Pharmaceutical Abstracts (until May 2008), Current Controlled Trials (with links to other databases of ongoing trials), UK National Research Register, USA - Centre Watch Clinical Trials Listing Service, and USA - National Institutes of Health, were searched.

The Website of the ADA and the UK diabetes Website were searched for abstracts of recent meetings. More studies were sought by scanning the reference lists of included trials, systematic reviews, meta-analyses and health technology assessment reports. Publishers of relevant trials and experts were contacted in order to obtain more references and reports of unpublished or ongoing trials. Studies published in any language were included.

Identification of eligible studies
Two authors independently reviewed the title, abstract or both sections of every record retrieved. A predetermined relevance form was used containing the inclusion and exclusion criteria. Full articles were also retrieved for clarification when there was doubt about their eligibility. If there was no agreement on a specific point, it was discussed until consensus emerged. An adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection was used.[7] A Kappa test of agreement was measured.

Data extraction and quality assessment
For studies fulfilled the inclusion criteria, two authors independently extract data using standard piloted data extraction templates. Any disagreements were resolved by discussion. Any relevant missing information on the trial was sought from the original authors of the article, if possible. The methodological quality of each randomised controlled trials (RCTs) was assessed independently by two authors using the National Health System Centre for Reviews and Dissemination (NHS CRD) checklist. Possible disagreements were resolved by consensus.

Assessment of heterogeneity
Heterogeneity was identified by visual inspection of the forest plots by using a standard χ^2-test and a significance level of a = 0.1, $P < 0.1$ in view of the low power of such tests. Heterogeneity will also be examined with I^2, where

I^2 values of 50% and more indicate a substantial level of heterogeneity.[8] When heterogeneity is found, we attempted to determine possible reasons by examining each study characteristics. The main method of synthesis of results was quantitative using Review Manager Software version 5.[9] Both fixed-effect and random-effect analysis were used, however, because of the heterogeneity only the result of random-effect analysis will be reported.

Included and excluded studies

Figure 1 shows details of the process of inclusion and exclusion of studies. Out of 1825 studies retrieved, 1752 were rejected because of irrelevance. From the remaining 73 studies, 20 were excluded as duplicates from different databases, 7 were excluded due to inappropriate population, 3 were excluded due to inappropriate study designs, 4 were excluded because of inappropriate intervention and 36 were excluded because of being review articles. Eventually, 3 trails met the inclusion criteria; two trails were completed[10,11] and one was an on-going trial. [12] For the on-going study, results were still blinded. Only the two completed RCTs were included in the analyses. The result of kappa test was 0.83, which is an excellent level of agreement.

The characteristics of the trails, inclusion and exclusion criteria, and characteristics of patients entered, and information about measurements are shown in Table 1. They support the character of the group to whom the results of the trials can be generalised. From the viewpoint of generalizability, it is notable that in both trials the patients were multinational. Also the ratio of females to males was 2:1, which is consistent with the nature of this
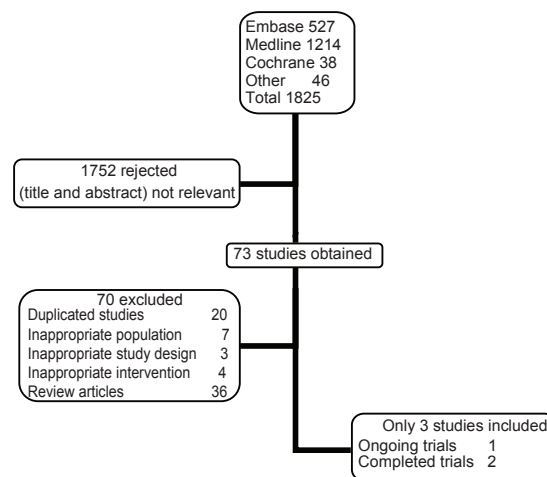

Figure 1: Flow diagram of included and excluded studies

Table 1: The characteristics of the included trails

Characteristic	Glimepiride trial[4]	Placebo trial[6]
Inclusion criteria	Age range = 8-17. T2DM. HBA1c >7.1. Negative to islet cell antibodies. C-peptide level >1.5 ng/ml. FBS level not stated (should be more than 126 mg/dl). Consent form.	Age range = 8-16. T2DM. HBA1c >7. C-peptide > 1.5 ng/ml. BMI > 50th percentile. FBS level 126-240 mg/dl. Consent form.
Exclusion criteria	History of acute metabolic decompensation. Current insulin treatment. On weight reduction treatment. Positive immune marker for T1DM. Hypersensitivity to diabetic medication. Patient on chronic medication which can affect glucose states, such as steroids.	History of acute metabolic decompensation. Current insulin treatment or received metformin within 3 months. Positive immune marker for T1DM. Hypersensitivity to diabetic medication. Serious diseases or chronic diarrhea which can affect the participants. Renal insufficiency, hepatic dysfunction.
Number of participants [intervention/control]	131/132	42/42
Male [intervention/control]	44/44	12/13
Female [intervention/control]	87/88	30/27
Age (mean ± SD) [intervention/control]	13.8 ± 2.3/13.8 ± 2.3	14/14
Ethnicity [intervention/control]	110/115	25/27
Cholesterol (mmol/l) [intervention/control]	Not given.	4.5/4.9
LDL (mmol/l) [intervention/control]	Not given.	2.6/2.9
HDL(mmol/l) [intervention/control]	Not given.	1.1/1.1
TGL (mmol/l) [intervention]	Not given.	1.7/2.3
similarity of groups at the baseline	Yes	No
HbA1c (mean ± SD) [intervention/control]	8.54 ± 1.57/8.52 ± 1.58	8.3 ± 1.3/9 ± 1.4
Fasting blood/plasma glucose (mean ± SD) [intervention/control]	172 ± 70.7/174.4 ± 66.7	9.2 ± 2.8/11 ± 3.3
Weight (kg)% [intervention/control]	83.83 ± 27.47/82.6 ± 25.60	92.8 ± 31.8/90.3 ± 38.1
BMI (kg/m²) % [intervention/control]	31.60 ± 8.17/31.57 ± 8.48	34.2 ± 10.6/33.9 ± 12.7

disease. A further interesting observation is that there was no similarity between the two groups in the placebo trial, but there was a clear difference between the HBA1c and FBS in the placebo group and the metformin group. In the glimepiride trial the authors did not give the result of the lipid profile but pointed out that there was no difference between the two groups at the start of the trial. In both trails the duration and severity of the diseases in intervention and control group was not mentioned.

The outcomes measured of the glimepiride trial were as follows: The primary efficacy outcome measured was the mean change in HBA1c from the baseline to the end of the study. The secondary efficacy outcome measures were as follows: mean change in HBA1c at week 12; proportion of subjects reaching the control goal of DM, which is HBA1c <7%; mean change in FBS from the baseline at weeks 4,8,12,18, and 24; mean change in lipid profile and change in BMI. The other important outcome measured was the safety of metformin and glimepiride which included a variety of adverse events.

The placebo trial, for its part, measured the following outcomes: The primary efficacy outcome measured was the mean change in FBS from the baseline. The secondary outcomes were mean changes in the HBA1c, BMI and lipid profile. Also a variety of adverse events were included in the study outcomes.

Quality of included studies

To decide if the included studies were good or poor in quality we used the following criteria: all the quality criteria met: good quality; one or more of the quality criteria only partially met: moderate quality; one or more criteria not met: poor quality, which indicated high risk of bias.

The quality of the included trials was poor. In the glimepiride trial the authors had not stated that the two interventions were indistinguishable or used any word which suggested a similar meaning. In both trial the word 'randomisation' was used, but without any explanation. Concealment was not mentioned in either trial. Blinding was not mentioned in both trails, probably because the outcomes measured were objective. However, blinding is still important whether the outcome is objective or not.

The two groups in the trials seemed to be treated similarly during the follow-up period. But in the placebo trial more than 50% of the patients in the placebo arm converted to the metformin arm, due to the failure of treatment. Most of them converted before week 6 but their results were analysed according to Intention to treat (ITT) analysis. The glimepiride trial was not conducted according to the ITT analysis.

Heterogeneity between the results of the trials

From the start and based on a detailed analysis of the characteristics of the placebo trail and glimepiride trail, the authors did not consider that it would be reasonable to get a combined summary estimate. This was mainly because the comparator in the placebo trail was a placebo, which is very different from the comparator in the glimepiride trail which was glimepiride.

Glycaemic control
Change in HGA1c
Figure 2 shows that in the glimepiride trial, there were significant reductions of mean change of HBA1c from baseline in both arms; it reduced by -0.71% (P = 0.0002) in the metformin group and by -0.54% (P = 0.001) in the other. In addition, more patients (48.1%) in the metformin group had achieved good glycaemic control (<7%) at week 24. In the placebo trial, the metformin group achieved significant improvements in glycaemic control and there was significant reduction in the adjusted mean HBA1c, from baseline 7.5 vs. 8.6 for metformin and placebo, respectively. The mean difference was -1.10 (95%CI of -1.19 to -1.01) which was significant and precise. When the reviewers recalculated the result using the ITT analysis principle and then repeated the meta-analysis for the glimepiride trial, a similar result was attained with same heterogeneity Chi^2 = 86.22, I^2 = 99% and P value <0.00001.

Fasting plasma glucose
In the glimepiride trial, the mean changes in fasting plasma glucose (FPG) from baseline were not significantly different in the glimepiride group; -14.6% and 15.1 % for week 18 and week 24 respectively. In the placebo trial, there was a significant reduction in the adjusted mean of FPG from baseline in the metformin group while there was an increase in the placebo group; -42.9 mg/dl vs. +21.4mg/dl (P value <0.001) with mean difference of -64.80 in favour of the metformin group.

Weight Change (BMI)
In the glimepiride trial, significant differences at week 12 were 0.07 kg^2 vs. 0.55 kg^2 for metformin and glimepiride respectively (P value < 0.001). These significant differences were also observed at week 24.

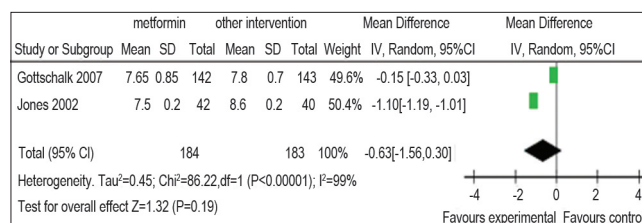| Study or Subgroup	metformin			other intervention			Weight	Mean Difference IV, Random, 95%CI	Mean Difference IV, Random, 95%CI
	Mean	SD	Total	Mean	SD	Total			
Gottschalk 2007	7.65	0.85	142	7.8	0.7	143	49.6%	-0.15 [-0.33, 0.03]	
Jones 2002	7.5	0.2	42	8.6	0.2	40	50.4%	-1.10[-1.19, -1.01]	
Total (95% CI)			184			183	100%	-0.63[-1.56,0.30]	
Heterogeneity: Tau^2=0.45; Chi^2=86.22,df=1 (P<0.00001); I^2=99%									
Test for overall effect Z=1.32 (P=0.19)									

Figure 2: Forest plot of comparison: HBA1C, outcome: mean change in HBA1C from baseline with ITT

But, when adjusted, the two groups were comparable. The mean difference was -0.56 with 95%CI of -2.57 to 1.45, which is not significant. In the placebo trial, there was no significant difference between the two groups; the mean difference was -0.2 with 95%CI of -2.33 to 1.44, which is wide and not significant [Figure 3]. After recalculating the result of the glimepiride trial with ITT analysis, the same mean difference was observed, but with a slight change in 95% CI. Overall, there was no significance in the result.

Lipid profile

In the glimepiride trial there was no significant difference seen between metformin and glimepiride. In the placebo trial Total Cholesterol decreased from the baseline level in the metformin patients with a slight increase in the placebo group. There was significant decrease in LDL levels in the metformin group. No significant changes were found in the other lipid parameters after adjusting. After recalculating the results using the ITT principle, no change in the results could be detected. The results are heterogeneous, as expected, and at this stage there are not sufficient grounds for using a summary effect estimate obtained by combining the results of the two trails. There was no subgroup analysis in either of trials.

Adverse events

The two trails[10,11] were of short duration; lasted only from 16 weeks to 24 weeks, therefore it was difficult to assess the adverse events of metformin and the chronic complications of T2DM in children. For this reason three retrospective and cohort studies were identified by which to assess the adverse events and chronic complications of type 2 DM in children. All these studies are based on small sample sizes, ranging from 42 to 72 participants. Benavides *et al*.[13] conducted a retrospective study with duration of 52 weeks to assess the safety of drug treatment for T2DM in children and adolescents. He concluded that patients managed with drugs had a significant decrease in HBA1c values, from 10.6% ± 2.7% (mean ± SD) before treatment to 8.0% ± 2.0% (*P* <0.001). Adverse reactions attributed to drugs included hypoglycaemia and gastrointestinal distress.

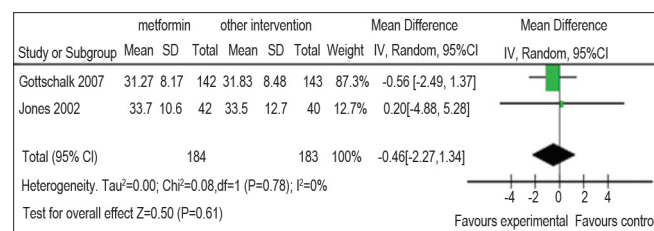In our included trials there was no death related to the treatment or to the T2DM. In the glimepiride trial, there were two serious adverse events, one in each arm. The incidence of clinical hypoglycaemia was between 10.6% and 8.5%, which is not significant, while in the placebo trial there were five severe adverse events, two in the metformin group and three in the placebo group. None linked to the interventions.

In the glimepiride trial there was 57.7% of adverse events in the metformin group compared with 59.2% in the glimepiride group. The risk ratio was 0.98 with 95%CI of 0.81 to 1.20, which is a non significant value. In the placebo trial there was 70% of adverse events in the metformin group and 60% in the placebo group. The risk ratio was 1.15 with 95% CI of 0.83 to 1.59, which means that there were 15% more adverse events in the metformin group, but this is still not significant because it can be translated as 17% fewer adverse events in the metformin group compared with as many as 59% more adverse events in the metformin group [Figure 4].

DISCUSSION

The burden of diabetes in children and adolescents is greater than that in adults as shown by Dean *et al*, who found that the mortality rate was 9%; micro albuminuria 35%; ESRD 6%; hypertension 45% and miscarriage in 38% of the females who had become pregnant.[14] Over the follow-up period, 35% were non complaints and, of those who followed the regime, 67% had poor glycaemic control (HBA1c of 10.9%). In Australia, also, it was found that adolescents with T2DM had significantly higher rates of high blood pressure and micro albuminuria, even with a shorter duration of T2DM.[15] As mentioned, the non-compliance in children more than in the adults support the need for a simple regimen, non- injectable like metformin, to increase the rate of compliance which probably will lead to better glycaemic control.

The limited number of studies is the major limitation for this review. Despite the extensive search, only 3 studies were identified and 2 of them were included. This led to an inability to assess the publication bias. The result may be influenced by several important aspects
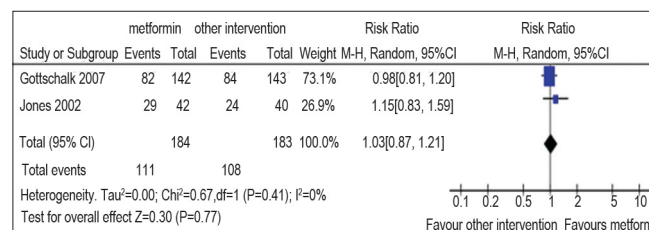

Figure 3: Forest plot of comparison: BMI, outcome: mean change in BMI from baseline with ITT

Figure 4: Forest plot of comparison of total adverse events in both trails

of trial design and the poor quality. The randomisation seems to have failed in the placebo trial, judging by the difference in baseline characteristics. As the placebo trial and glimepiride trial examined markedly different comparators (i.e. a placebo vs. glimepiride), the authors expected great heterogeneity. The duration of both studies was very short, which is another limitation in assessing the long-term complications and the safety of metformin. Another limitation is in the placebo trial: more than 65% in placebo group failed to achieve glycaemic control, causing the two-armed trial to stop and resumed as a one-armed trial. The metformin was effective for glycaemic control of diabetic patients if compared with a placebo or diet and exercise but was only marginally more effective than glimepiride (no significant difference). The other limitation is in the glimepiride trial, where weight was measured using BMI, which in children is not accurate indicator of body weight.

Heterogeneity was one of the major limitations in this SR. As a general role the clinical heterogeneity will lead to statistical heterogeneity because from the start and based on a detailed analysis of the characteristics of the placebo trail and glimepiride trail, we did not consider that it would be reasonable to get a combined summary estimate. This was mainly because the comparator in the placebo trail was a placebo, which is very different from the comparator in the glimepiride trail which was glimepiride which will lead to an obvious heterogeneity.

The best way to resolve many of doubts and limitations identified would be to perform a large, multicentre, double-blind RCT assessing not just impact on efficacy and adverse events, but also directly measured quality of life. The study should be powered to detect important differences in patient quality of life. Health economic study should be conducted in parallel, with particular scrutiny being directed to the magnitude of potential costs averted by metformin such as weight, lipid and hypertension reduction.

CONCLUSION

There was limited but not convincing evidence to suggest that metformin can improve the glycaemic control in children and adolescent with type 2 diabetes compared with other interventions. The limited number, poor quality and short duration of the included trials are among limitations of this review. This review can be updated after the results of the third trails or new trails published.

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